USSN: 09/616,283; Art Unit: 1645
Attorney Docket No. VRXB-P01-001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

GOODNOW

Serial No: 09/616,283

Filed: July 14, 2000

For: SYSTEM FOR DETECTING BACTERIA IN BLOOD, BLOOD PRODUCTS, AND FLUIDS OF TISSUES

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Art Unit: 1645

Attorney Docket No. VRXB-P01-001

Examiner: J. Hines

Assistant Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Declaration Under 35 U.S.C. §1.132

Sir:

I, Harvey G. Klein, MD., hereby declare as follows:

1. I am the Chief of the Department of Transfusion Medicine at the Warren C. Magnuson Clinical Center, National Institutes of Health. I have been conducting research in the field of transfusion medicine for over thirty (30) years. I serve on the Food and Drug Administration's (FDA) Blood Products Advisory Committee. I actively hold leadership positions in the American Association of Blood Banks, the American Blood Commission, the American Society of Hematology, and the American Society of Apheresis. I currently serve as Chairman of the Committee of Revision for Blood and Blood Products for the U.S. Pharmacopeia. I am a diplomat of the American Board of Internal Medicine and a diplomat of the American Board of Pathology. I have authored and co-authored

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more than 175 publications on transfusion medicine. Accordingly, my curriculum vitae is attached as Appendix A.

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2. I have read the above-identified application, the pending claims, and the Office Action mailed on September 29, 2003.

3. I understand that the Examiner has stated that the invention as described and claimed in the above-identified application is obvious in view of the teachings of Fisher et al. WO 98/57994, McLaughlin (U.S. Patent 4,683,196), Tadler et al. (*J. Clin. Lab. Anal.* 3: 21-25 (1989)), Erich et al. (*J. Immunol.* 143(12): 4053-4060, 1989), and Chang et al. (U.S. Patent 5,200,323).

4. For the reasons stated below, I respectfully disagree with the Examiner. I have been working in the field of transfusion medicine for over thirty (30) years and over the past two decades the issue of bacterial contamination has been a source of primary concern for blood collectors and transfusion service scientists and clinicians. It is estimated that as many as one in 12,000 transfusions lead to a severe septic reaction and as many as one in 46,000 transfusions can lead to death due to bacterial contamination. In the recent years, it has been further reported that an unexpectedly large number of deaths were attributed to bacterial contamination/sepsis. For example, the fatality rate for transfusion related bacterial sepsis during the period from 1999 to 2002 averaged more than 15%.[1]

(a) [1] People's Choice Award - 2003 FDA Science Forum; "Transfusion Related Fatalities from Bacterial Contamination of Blood Components," L.E.Simmons, MT(ASCP)[1], M.A.Knippen[2], L.G.Holness, M.D.[3], [1]OCBQ, CBER, FDA, Rockville, MD, [2]OCBQ, CBER, FDA, Rockville, MD, [3]OBRR, CBER, FDA, Rockville, MD

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Although, blood banks routinely test each unit of donated blood for human immunodeficiency virus (HIV), hepatitis B and C virus, syphilis, and Human T-cell Lymphotrophic Virus (HTLV) and discard units which have abnormal test results, they do not test for bacterial contamination because of the lack of a safe and effective test.[2] Accordingly, the nation's leading blood safety experts have been repeatedly calling for immediate action from the blood banking community to initiate a program to detect the presence of bacteria in blood and blood products.

5. As early as 1992, P. Ann Hoppe[3] reported that that although numerous studies had been performed by the FDA and others, no rapid and reliable tests existed that could be readily applied in the blood bank setting. See Transfusion 1992; 32(3): 199-201.

6. In December 1997, a multi-center study for the systematic collection of data concerning bacterial contamination of blood components (BaCon Study) was initiated under the guidance of the American Association of Blood Banks (AABB), the American Red Cross (ARB), and the Center for Disease Control and prevention (CDC). The goals of this study included determining the rates of bacterial contamination associated with recipient transfusion reactions, identification of responsible micro-organisms, and identification of risk factors for bacterial contamination.

7. On February 23, 1999, Jane Henney, the FDA commissioner testified as follows before the U.S. House of Representatives in a hearing on issues of blood safety: "The safety and

[2] American Red Cross web site on safety of donated blood: www.givelife2.org/donor/bloodsafety.asp. See Appendix B

[3] The Acting Director, Division of Transfusion Science of the FDA.

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adequacy of the blood supply and blood products is one of the highest priorities of the FDA and the Department of Health and Human Resources. . . For a number of serious and life-threatening infections, there is a limited period after a possible donor has been infected, which the infection is not detectable by available methods. ... The risk to patients from bacterial contamination of blood and from blood band error must also be reduced."

8. Despite this long felt need and high level of interest in the field for a rapid and effective screening assay to detect clinically relevant amounts of bacteria in blood and blood products, to the best of my knowledge no such reliable test is currently on the market. In fact, due to the lack of such reliable testing methods, the Food and Drug Administration (FDA) guidelines require shorter storage times as a means for controlling the increase in bacterial contamination upon storage. However, the trade-off is reduced blood availability.

9. I list below certain tests that have been developed over the past two decades in an effort to alleviate this problem. However, none of these have proven to be effective in detecting clinically relevant amounts of bacteria.

- RNA probes were developed as universal probes to detect bacterial contamination; however, this method was too cumbersome for routine blood bank screening and was associated with a high rate of contamination. These probes are no longer being marketed by the manufacturer.

- Visual inspections also did not prove to be a useful method for detecting bacterial contamination.

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- Testing for glucose levels was not found to be a viable alternative because certain contaminants like *S. epidermis*, a common skin contaminant, grows slowly and glucose changes could not be detected until later in the storage period.

- Filtration methods had no impact on the bacterial levels – in no case were the bacteria eliminated, and in fact, bacteria reached the same titer at the stationary phase of growth, whether or not the pool was filtered.

- Certain antigen detection systems using latex agglutination, fluorescent antibody stains, and enzyme-linked immunosorbent, are available, however, these methods have been plagued with variable sensitivity and specificity. As taught in the Verax application, an obvious concern with regards to detection of blood contaminants is the requirement of a ubiquitous microbial antigen to ensure detection of diverse bacterial species.

- Around the mid-1990s, the American Red Cross, in collaboration with a commercial company Binax, developed a prototype assay using immunological methods to detect bacterial contamination of blood components. The test was developed to detect the presence of a common microbial antigen, peptidoglycan, by immunochromatography. However, Binax subsequently abandoned the test due to its inability to detect all the bacteria implicated in platelet transfusions as peptidoglycans are not expressed on the surface of Gram negative bacteria.

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10. Therefore, to date, despite the repeated call for improved testing methodologies, and despite the numerous attempts to develop effective tests, there is no effective method for detecting bacterial contamination. I believe that the Verax test provides a non-obvious solution to meet this long-felt need in the blood banking arena.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the United States Code and that willful false statements may jeopardize the validity of this Application for Patent or any patent issuing thereon.

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Dated:_____ Signature: _____

Dr. Harvey G. Klein
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National Institutes of Health

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